The Spectrum of Pituitary Adenoma Hemorrhage

DENNIS D. HICKSTEIN, MD, *Seattle;* WILLIAM F. CHANDLER, MD, *and*
JOHN C. MARSHALL, MD, PhD, *Ann Arbor, Michigan*

In 34 cases of pituitary adenoma hemorrhage at one institution, the clinical manifestations of adenoma hemorrhage depended upon the size of the adenoma, the presence of suprasellar extension, the amount of hemorrhage and the extent of pituitary glandular destruction. Recognition of the spectrum of acute, subacute and chronic pituitary adenoma hemorrhage should expedite diagnosis and treatment.

(Hickstein DD, Chandler WF, Marshall JC: The spectrum of pituitary adenoma hemorrhage. West J Med 1986 Apr; 144:433-436)

Despite previous studies emphasizing the vascularity of pituitary adenomas, vascular events in pituitary adenomas are not commonly recognized in clinical practice. The classic form of pituitary adenoma hemorrhage, "pituitary apoplexy," features dramatic clinical symptoms with the sudden onset of severe headache, visual loss and, frequently, altered consciousness.[1,2] Rapid evacuation of the hemorrhagic pituitary adenoma may reverse the visual loss and preserve life. As a result, pituitary apoplexy is recognized as an acute neuroendocrine emergency.

That lesser degrees of pituitary adenoma hemorrhage can lead to clinical deterioration has not been widely appreciated. In this report we describe hemorrhage and hemorrhagic necrosis in 22% of pituitary adenomas removed at one hospital over an 11-year period. Comparison of the operative and pathologic reports with the clinical symptoms enabled us to delineate a spectrum of acute, subacute and chronic pituitary adenoma hemorrhage.

Patients and Methods

We did a retrospective analysis of 154 patients who underwent hypophysectomy for removal of a pituitary adenoma at the University of Michigan Hospital between January 1, 1970, and December 31, 1980. Review of the operative reports and pathologic specimens documented hemorrhage or hemorrhagic necrosis within the adenoma. The clinical presentation and radiographic findings were obtained from a detailed chart review.

Results

Clinical Features

The 34 patients with pituitary adenoma hemorrhage were separated into three groups based on the presentation and duration of symptoms (Table 1). Ten patients presented with symptoms of acute pituitary adenoma hemorrhage consistent with classic pituitary apoplexy. This diagnosis required the acute onset of severe headache, visual loss, cranial nerve palsies or altered consciousness; radiographic documentation of an intrasellar or suprasellar mass, and demonstration of hemorrhage or hemorrhagic necrosis of a pituitary adenoma on pathologic examination.[3]

Patients with acute symptoms of pituitary adenoma hemorrhage were seriously ill. Nine had the sudden onset of severe headache, which prompted medical consultation within hours of its onset. In seven of the eight patients who had visual loss, a hemianopia was present. In addition, seven patients had a temperature greater than 38.5°C (101.3°F), six were confused and cranial nerve palsies developed in three. The only patient in the acute group without headache and visual loss presented with hypotension and syncope from adrenal insufficiency due to the loss of adrenocorticotropic hormone following hemorrhage into a pituitary adenoma.

In all, 24 patients with pituitary adenoma hemorrhage presented with less acute symptoms. Five patients presented on seven occasions with headache and visual loss evolving over two weeks to four months. On each occasion a hemorrhagic pituitary adenoma was removed at operation. These patients did not manifest the fever or altered mental state seen with acute pituitary adenoma hemorrhage, nor was disturbance of endocrine function a characteristic feature of this group.

A total of 19 persons with pathologic evidence of pituitary adenoma hemorrhage or necrosis presented with symptoms primarily related to an endocrine disorder, usually galactorrhea-amenorrhea. Although these patients had had symptoms for greater than four months, many reported exacerbations of symptoms within this time.

From the Department of Medicine, University of Washington School of Medicine, Seattle (Dr Hickstein), and the Departments of Medicine (Dr Marshall) and Neurosurgery (Dr Chandler), University of Michigan Medical Center, Ann Arbor.

Presented in part at the American College of Physicians Annual Meeting, San Francisco, April 13, 1983.

Reprint requests to Dennis D. Hickstein, MD, Bldg 13, Rm 112 (GMR 151), Veterans Administration Medical Center, 1660 South Columbian Way, Seattle, WA 98108.

Pituitary adenoma hemorrhage developed against a background of prior radiation therapy in persons with both subacute and chronic symptoms (Table 1). Notably, none of the ten patients with acute onset of symptoms had received prior radiation therapy to the pituitary.

Roentgenographic Studies

Enlargement of the sella turcica on lateral skull x-ray film was present in all of the patients with acute and subacute symptoms and in nearly 90% of those with chronic symptoms (Table 1). The abnormalities on the skull film frequently led to further diagnostic studies to evaluate the pituitary fossa.

TABLE 1.—*Features of Patients With Pituitary Adenoma Hemorrhage*

Patient Characteristic	*Acute*	*Subacute*	*Chronic*
Patients, No.	10	5	19
Episodes, No.	10	7	19
Age, years (mean)	39.7	49.4	37.6
(range)	28-74	39-64	20-58
Sex (female/male)	5/5	3/2	14/5
Presenting symptoms			
Headache and/or visual loss	9/10	7/7	6/19
Endocrine disorder	1/10	0	13/19
Duration of symptoms			
Less than 48 hours	8/10	0	0
48 hours to 2 weeks	2/10	0	0
2 weeks to 16 weeks	0	7/7	0
More than 16 weeks	0	0	19/19
Enlarged sella turcica on skull film	10/10	7/7	17/19
Suprasellar extension of adenoma	9/10	6/7	9/19
Previous radiation therapy	0/10	2/5	3/19
Pathologic specimen			
Hemorrhage (>5ml)	1/10	7/7	0
Hemorrhagic necrosis	10/10	7/7	19/19

Computed tomography (CT) of the head showed a suprasellar mass in all five patients in the acute group in whom it was done. Hemorrhage or necrosis of the mass was described in four of the five scans. Only one patient in the subacute group had a CT scan. The study showed hemorrhage and necrosis of a suprasellar mass. Four patients in the chronic group had CT scans. A suprasellar mass was present in three patients, one of which contained radiographic evidence of hemorrhage. The CT scan in the fourth person showed an empty sella. Two CT scans illustrate the differences in the appearance of pituitary adenoma hemorrhage depending on timing of the CT scan and extent of the hemorrhage (Figures 1 and 2).

Because many of the patients were evaluated before the time when CT scans of the head were available, pneumoencephalography played an important role in showing suprasellar extension of pituitary adenomas. Adenomas with suprasellar extension accounted for 85% to 90% of those in the acute and subacute groups, whereas only 50% of the adenomas in the chronic group extended above the sella (Table 1).

Endocrine Function and Pathology

The effect of adenoma hemorrhage on endocrine function varied, depending on the duration of symptoms and the extent of glandular destruction. In the patients with acute onset of symptoms, three presented with evidence of endocrine-active (secretory) adenomas. The remaining persons in this group had endocrine-inactive (nonsecretory) adenomas. All adenomas were nonsecretory in the subacute group. In contrast,

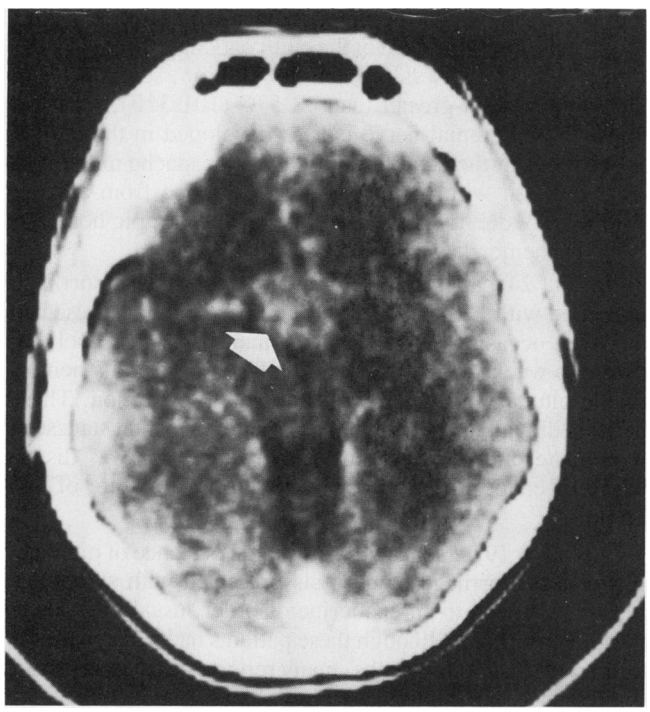

Figure 1.—Computed tomographic scan of the head (without contrast) done within hours of the onset of symptoms in a patient with an acute presentation of pituitary adenoma hemorrhage. This scan shows a high-density mass in the suprasellar region from hemorrhage into the adenoma **(arrow).**

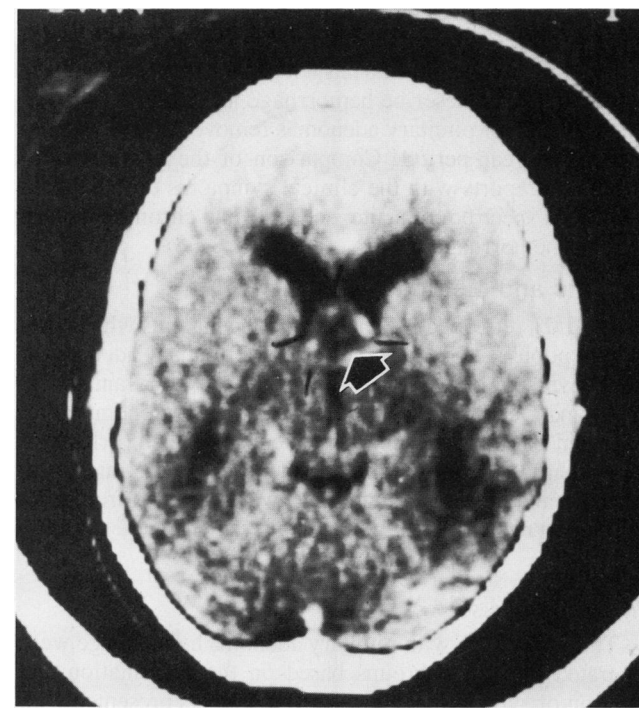

Figure 2.—A computed tomographic scan of the head done several days after the onset of symptoms of pituitary adenoma hemorrhage. A contrast-enhancing rim around a central, low-density, hemorrhagic-necrotic area is seen **(arrow).**

two thirds of the adenomas remained secretory in the group with chronic symptoms.

Extensive hemorrhage and necrotic debris permeated the adenomas from persons in all three groups (Figure 3). This extensive destruction of glandular tissue precluded accurate pathologic classification of adenoma type in most instances.

Management

All patients in this study underwent transsphenoidal or subfrontal removal of a pituitary adenoma. Nine of the ten patients in the acute group were treated with corticosteroids, including both patients with known adrenal insufficiency. Three of the four patients with hypothyroidism in this group received thyroid hormone replacement before their operation. There were no deaths and only one of the ten patients had a residual visual field defect.

In the group with subacute symptoms, all patients were treated with corticosteroids, and the two patients with hypothyroidism received thyroid hormone replacement before their operation. There was one death in this group from obstructive hydrocephalus due to recurrent pituitary adenoma.

In the group with chronic duration of symptoms, seven patients received corticosteroids before the operation. Five were placed empirically on corticosteroid therapy and two had adrenal hypofunction documented preoperatively. All but one of the patients with hypothyroidism received replacement therapy. There were no deaths and no persons with residual visual field defects in this group.

Discussion

This study showed a 22% incidence of hemorrhage and hemorrhagic necrosis in surgically removed pituitary adenomas. Patients with acute symptoms of pituitary adenoma hemorrhage presented within 48 hours of the onset of severe headache and visual loss. Those with subacute symptoms of adenoma hemorrhage presented with headache and visual loss evolving over a two-week to four-month period of time. In contrast, most patients with chronic adenoma hemorrhage appeared because of gradually progressive symptoms (greater than four months) of an underlying pituitary endocrine disorder.

Only two persons had adenomas that did not produce enlargement of the sella turcica on lateral skull roentgenograms. In six previous studies of acute pituitary adenoma hemorrhage, 52 of 54 patients had an abnormal sella turcica on lateral skull films.[2,4-8] Enlargement of the sella turcica did not provide any evidence of hemorrhagic or necrotic changes within the adenoma.

The clinical manifestations of pituitary adenoma hemorrhage depended on the size of the adenoma, the presence of suprasellar extension, the amount of hemorrhage and the extent of pituitary glandular destruction. These factors not only determined the clinical presentation, but they also influenced diagnostic studies and management.

The presence of suprasellar extension of a pituitary adenoma directly influenced the clinical presentation. When hemorrhage developed in an adenoma with suprasellar extension, headache and visual loss frequently occurred. These were the presenting complaints in all but one of the persons in the acute and subacute groups and nearly 90% had suprasellar extension of the adenoma. In contrast, only half of those with chronic symptoms had suprasellar extension of an adenoma. Headache and visual loss, present in a third of the persons in this group, were confined to those with suprasellar extension.

The preponderance of adenomas with suprasellar extension in the acute and subacute groups shows the efficacy of computed tomography of the head in these patients. CT scan not only showed the suprasellar mass, it also detected hemorrhage or necrosis within the mass. To detect hemorrhage, the scan had to be done within hours of the acute event.[9] If several days or weeks elapsed before the CT scan was done, pituitary hemorrhage and necrosis appeared as areas of low density in the region of the pituitary on a noninfusion scan. Contrast injection then resulted in a ring-like enhancement around this central core of low density.[10]

There was a wide range in the duration of symptoms be-

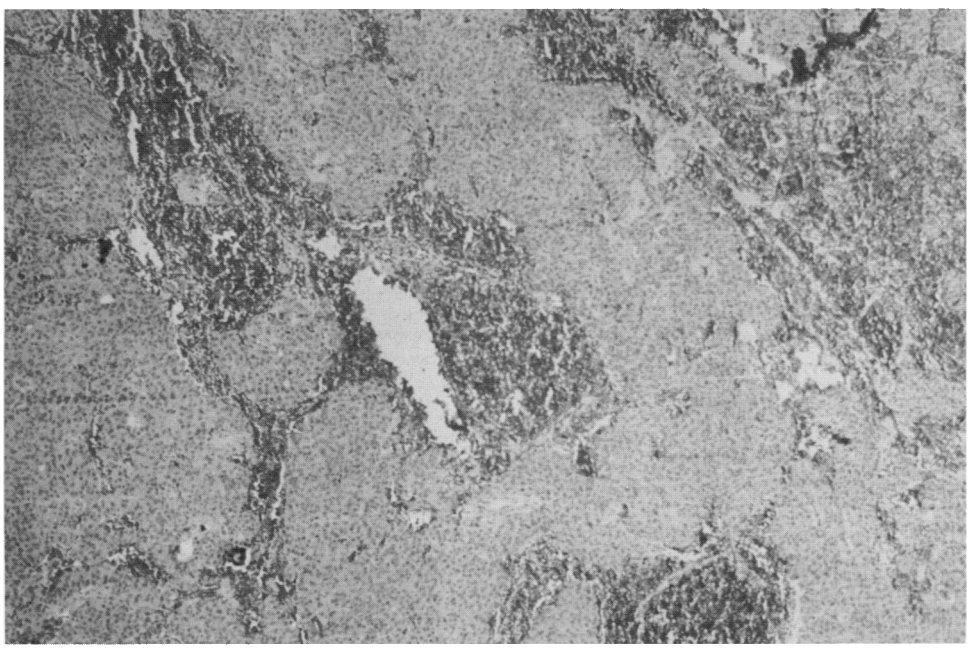

Figure 3.—Pituitary adenoma permeated by hemorrhage in a patient with acute pituitary adenoma hemorrhage (hematoxylin and eosin, magnification ×10).

fore presentation in all three groups. This suggested that suprasellar extension, although influencing the type of symptoms, was not the only factor responsible. The extent of adenoma hemorrhage most likely determined the tempo of symptoms.

Endocrine data from the three groups with pituitary adenoma hemorrhage in this study are notable for the persistence of selected hypersecretion by a hemorrhagic-necrotic adenoma. The elevations of growth hormone and prolactin levels in the acute and chronic groups may have resulted from release of hormone by the damaged gland. Evidence of multiglandular deficiency was common to all three groups. Whether the evidence of glandular hypofunction was due to the adenoma compressing parent cell types or due to hemorrhagic destruction of the parent cells is not known.

In a recent and comprehensive review of the literature on endocrine function after pituitary apoplexy, Veldhuis and Hammond described "pleuritrophic" anterior pituitary dysfunctions, in contrast to more selective trophic lesions.[11] Growth hormone was the most frequently encountered deficiency, occurring in 88% of patients. Diminished cortisol secretion occurred in 66% and reduced thyroid hormone secretion was found in 42% of patients. Hypothalamic dysfunction was present in four of their patients in whom extensive testing was done. This might reflect disruption of the hypothalamic-portal delivery of releasing factors rather than hypothalamic damage itself.

The type of pituitary adenoma prone to undergo hemorrhagic transformation remains controversial. When the topic was reviewed by Wright, he concluded that the occurrence of apoplexy was not increased in one particular adenoma type.[12] Others have concluded that hemorrhage occurs with a higher frequency in eosinophilic adenomas.[13] Frequently the extensive hemorrhage and destruction present in this condition precludes accurate histologic determination of adenoma type.

Management of pituitary adenoma hemorrhage usually depends on the type of symptoms, as well as their rate of progression. Initially, known or suspected hormone deficiencies are corrected. Progression of neurologic symptoms, especially visual loss, remains the major indication for emergent surgical evacuation of a hemorrhagic pituitary adenoma. Since this study required operative intervention for histologic confirmation of the diagnosis, it does not address the relative merits of medical versus surgical treatment of adenoma hemorrhage in situations where visual fields remain intact.

Search for a cogent explanation for pituitary adenoma hemorrhage has produced several theories. Initially it was suggested that rapid adenoma growth led to infarction due to inadequacy of the blood supply relative to tumor size.[13] This appeared unlikely because adenomas exhibiting hemorrhagic changes were slow growing and showed an absence of unmistakable anaplasia histologically. In addition, hemorrhage and infarction occurred in some small adenomas, which argued against the vascular mismatch theory. Adenoma size played a dominant role in later explanations. Dawson proposed that lateral growth of the adenoma gradually occluded the cavernous sinus, raising the venous pressure in the pituitary and leading to hemorrhage.[2] Rovit and Fein suggested that tumor expansion in the sella turcica led to compression of the blood supply to the pituitary at the notch of the diaphragma sellae, producing relative ischemia in the anterior lobe of the pituitary.[7] Although these etiologies may be important in large tumors, they do not explain the occurrence of hemorrhage and infarction in many of the relatively small adenomas in the group with chronic symptoms. A more likely explanation for the development of adenoma hemorrhage has been advanced by Muller and Pia.[14] They believed that adenomatous blood vessels simply were more vulnerable to hemorrhage. Degenerative change in pituitary adenomas with hemorrhage, necrosis and cyst formation is postulated to develop from multiple, discrete episodes of pituitary hemorrhage.[15]

While it is recognized that acute hemorrhage into a pituitary adenoma with suprasellar extension produces dramatic symptoms, it is not well recognized that lesser degrees of hemorrhage in similar or smaller sized adenomas produce less dramatic symptoms, which evolve over a period of weeks to months. Recognition of this propensity of pituitary adenomas to undergo hemorrhagic transformation may expedite the diagnosis in persons presenting with headache and visual loss, and it may explain a sudden neuroendocrine deterioration in a patient with a known pituitary adenoma.

These data provide clinical support for the observation expressed by Jefferson more than 40 years ago: "So vascular are many adenomas that the wonder is that hemorrhages are not more common."[1]

REFERENCES

1. Jefferson G: Extrasellar extensions of pituitary adenomas (President's address insert). Proc R Soc Med 1940; 33:433-458

2. Dawson BH, Kothandaram P: Acute massive infarction of pituitary adenomas: A study of five patients. J Neurosurg 1972; 37:275-279

3. Weisberg LA: Pituitary apoplexy: Association of degenerative change in pituitary adenoma with radiotherapy and detection by cerebral computed tomography. Am J Med 1977; 63:108-115

4. Conomy JP, Ferguson JH, Brodkey JS, et al: Spontaneous infarction in pituitary tumors: Neurologic and therapeutic aspects. Neurology (Minneap) 1975; 25:580-587

5. David NJ, Glaser JS, Gargano FP: Pituitary apoplexy in clinical perspective, *In* Glaser JS, Smith JL (Eds): Neuro-ophthalmology: Symposium of the University of Miami and the Bascom Palmer Eye Institute. St. Louis, Mosby, 1975, pp 140-165

6. McDonald TS, Tolis G, McGarry EE: Twenty-two cases of pituitary apoplexy. Ann R Coll Phys Surg Can 1975; 8:9

7. Rovit RL, Fein JM: Pituitary apoplexy: A review and reappraisal. J Neurosurg 1972; 37:280-288

8. Sachdev Y, Evered DC, Hall R: Spontaneous pituitary necrosis. Br Med J 1976; 1:942

9. Post MJD, David NJ, Glaser JS, et al: Pituitary apoplexy: Diagnosis by computed tomography. Radiology 1980; 134:665-670

10. Fitz-Patrick D, Tollis G, McGarry EE, et al: Pituitary apoplexy—The importance of skull roentgenograms and computerized tomography in diagnosis. JAMA 1980; 244:59-61

11. Veldhuis JD, Hammond JM: Endocrine function after spontaneous infarction of the human pituitary: Report, review, reappraisal. Endocr Reviews 1980; 1:100-107

12. Wright RL, Ojemann RG, Drew JH: Hemorrhage into pituitary adenomata: Report of two cases with spontaneous recovery. Arch Neurol 1965; 12:326-331

13. Brougham M, Heusner AP, Adams RD: Acute degenerative changes in adenomas of the pituitary body with special reference to pituitary apoplexy. J Neurosurg 1950; 7:421-439

14. Muller W, Pia HW: Zur Klinik und Atiologie der Massenblutungen in Hypophysendadenome. Dtsch A Nervenheilk 1953; 170:326-336

15. Grant FC: The surgical treatment of pituitary adenomas. JAMA 1939; 113:1279-1282